

REMARKS

Reconsideration of the present application in view of the above amendment and the following remarks is respectfully requested. Claims 2-20, 27-43, 46-49, 52-55, and 58-61 are pending, of which claims 7-20, 33-34, 38-43, 46-49, 52-55, and 58-61 are withdrawn from consideration. Claims 2-4 have been amended to more clearly define certain aspects of the present invention. Support for such amendments may be found, for example, at page 16, liens 28-30. No new matter has been added.

Information Disclosure Statement

The Action states that submission of reference AG in the IDS filed March 29, 1999 is acknowledged and the signed accompanying 1449 form is attached. However, no 1449 form was found with the Action. Applicants respectfully request that the Examiner send the 1449 page acknowledging the cited reference.

Rejection Under 35 U.S.C. § 102(b)

Claims 2 and 5 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Bult *et al.* More specifically, the Action asserts that Bult *et al.* (*Science* 273: 1058-73, 1996) teach a 47mer protein that comprises the sequence IYSYV, thus comprising at least 5 consecutive amino acids of SEQ ID NO:1 (*i.e.*, Aaa-Baa-Ser/Ala-Tyr/Phe-Caa). The Action further states that because mouse claudin-1 has the amino acid I for position Aaa and the Amino acid Y for position Baa and mouse claudin-2 has V at position Caa, the 47mer disclosed by Bult *et al.* also meets the limitation “wherein Aaa, Baa and Caa indicate amino acid residues that are present in a naturally occurring claudin.”

Applicants have amended claim 2 to more clearly define the claimed subject matter. Amended claim 2 is now directed to a cell adhesion modulating agent that comprises at least five consecutive amino acid residues of a claudin CAR sequence, wherein the claudin CAR sequence is present in a naturally occurring claudin and has the formula set forth in SEQ ID NO:1. Thus, Aaa, Baa and Caa of SEQ ID NO:1 are required to be present in a single naturally occurring claudin. Because the 47mer does not contain a sequence that comprises at least five

consecutive amino acid residues as set forth in SEQ ID NO:1 and present in a naturally occurring claudin, Applicants submit that the Bult *et al.* reference does not anticipate the invention as presently claimed.

In view of the above remarks, Applicants submit that this ground of rejection under 35 U.S.C. § 102 has been overcome. Withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 2-6, 27-32 and 35-37 stand rejected under 35 U.S.C. § 112, first paragraph, as being allegedly not enabled. More specifically, the Action asserts that the specification is not enabling for the current claim scope because it does not disclose which subsequences of 5, 7 or 8 amino acids in length of SEQ ID NO:1 can modulate cell adhesion. In addition, the Action provides a BLAST search report to support its assertion that it has established a *prima facie* case of non-enablement. This report contains multiple proteins that comprise the sequence IYSY, but are not attributed to be involved in cell adhesion.

Applicants respectfully traverse this ground of rejection. Applicants submit that there is no sufficient evidence in the Action to support a *prima facie* non-enablement case in this application. First, the search report cited in the Action is insufficient for one of ordinary skill in the art to doubt the objective truth in the specification regarding the cell adhesion modulating agent as claimed in claim 5. This search report cited in the Action lists 46 proteins that comprise only *four* consecutive amino acids of SEQ ID NO:1 (*i.e.*, IYSY) present in a naturally occurring claudin, not *five* consecutive amino acids of SEQ ID NO:1 now present in a naturally occurring claudin as recited in claim 2. Applicants have conducted a similar search using *five* consecutive amino acids of SEQ ID NO:1 (*i.e.*, IYSYA) present in mouse claudin-1 as a query sequence. The search results, as well as the results of two other searches described in detail below, are enclosed in a Supplemental Information Disclosure Statement for the Examiner's convenience. The search produces a list of only 11 proteins, three of which are claudin-1. Second, the proteins other than claudin-1 that comprise IYSYA obtained from Applicants' search contain at least 150 consecutive amino acids, which are much larger than that of the claimed cell adhesion modulating agent. The extra portions of these proteins may alter or modify the functions of the

portions that comprise IYSYA. Thus, the search report cited in the Action is insufficient for establishing a *prima facie* case of non-enablement regarding claim 5.

In addition, the search report cited in the Action is insufficient for doubting the objective truth of the present specification regarding the cell modulating agent as claimed in claim 7. Applicants have conducted BLAST searches using sequences consisting of *seven* consecutive amino acids of SEQ ID NO:1 (*i.e.*, WKIYSYA or KIYSYAG) present in mouse claudin-1 as query sequences. The search using the sequence WKIYSYA as the query sequence identifies only claudin-1 as comprising the exact query sequence, whereas the search using the sequence KIYSYAG as the query sequence identifies various claudin-1 molecules as comprising the exact query sequence with a putative RNA dependent RNA polymerase as the only exception. Thus, one of ordinary skill in the art would not doubt that an agent (*e.g.*, a peptide) that comprises at least *seven* consecutive amino acid residues of SEQ ID NO:1 has a cell adhesion modulating activity, based on the search report cited in the Action that uses only a sequence consisting of *four* consecutive amino acid residues of SEQ ID NO:1 as a query sequence.

Similarly, the search report cited in the Action is insufficient for doubting the objective truth of the present specification regarding the cell modulating agent as claimed in claim 7. Because the search, using the sequence WKIYSYA as a query sequence, identifies only claudin-1 as comprising the exact query sequence, a search using the sequence WKIYSYAG, an exemplary SEQ ID NO:1, would only identify claudin-1 molecules as comprising the exact query sequence. Thus, one of ordinary skill in the art would not doubt that a composition (*e.g.*, a peptide) that comprises at least *eight* consecutive amino acid residues of SEQ ID NO:1 has a cell adhesion modulating activity, based on the search report cited in the Action that uses only a sequence consisting of *four* consecutive amino acid residues of SEQ ID NO:1 as a query sequence.

Regarding the concerns related to the identities of the subsequences of 5, 7, or 8 amino acids in SEQ ID NO:1 required for the cell adhesion modulating activity of an agent that comprises the subsequences, as an initial matter, Applicants respectfully submit that such concerns are not relevant to the subject matter of claim 4. Claim 4 recites that the cell adhesion modulating agent comprises at least eight consecutive amino acid residues of SEQ ID NO:1. Because SEQ ID NO:1 consists of eight consecutive amino acid residues, all of these residues are

required to be present in the cell adhesion modulating agent according to claim 4. As to claim 3 directed to a cell adhesion modulating agent comprising at least seven consecutive amino acid residues of SEQ ID NO:1, Applicants submit that in view of the teachings of the present application, one of ordinary skill in the art would know that the claimed cell adhesion modulating agent may comprise either Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa or Lys/Arg-Ass-Baa-Ser/Ala-Tyr/Phe-Caa-Gly. Similarly, as to claim 2 directed to a cell adhesion modulating agent comprising at least five consecutive amino acid residues of SEQ ID NO:1, Applicants submit that in view of the teachings of the present application, one of ordinary skill in the art would know that the claimed cell adhesion modulating agent may comprise any of the five consecutive amino acid residues of SEQ ID NO:1.

Applicants further submit that the present application provides sufficient guidance for one of ordinary skill in the art to make and use the claimed invention without undue experimentation. More specifically, the present application now claims a cell adhesion modulating agent that comprises at least five, seven or eight consecutive amino acid residues of a claudin cell adhesion recognition (CAR) sequence, wherein the CAR sequence is present in a naturally occurring claudin and has the format set forth in SEQ ID NO:1. Because these five, seven or eight consecutive amino acid residues are present in a naturally occurring claudin, the number of the sequences consisting of these residues are limited. Thus, one of ordinary skill in the art, in view of the teachings provided by the present application, may readily make various agents that comprise the above sequences, and further screen for agents that have cell adhesion modulating activities through routine experimentation. The teachings for making the claimed agents may be found at page 16, line 25 to page 37, line 3 and Example 1 of the present application; and the teachings for evaluating the cell adhesion modulating activities of candidate agents may be found at page 38, line 21 to page 43, line 31 and Examples 2-4 of the present application.

In view of the above remarks, Applicants submit that this ground of rejection under 35 U.S.C. § 112, first paragraph, has been overcome. Withdrawal of this rejection is respectfully requested.

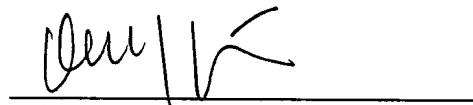
Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**" Also enclosed is a copy of updated Limited Recognition Under 37 CFR § 10.9(b).

On the basis of the above amendments and remarks, reconsideration of the application and its allowance are respectfully requested. Should the Examiner have any additional questions, she is respectfully encouraged to contact the undersigned attorney at (206) 622-4900.

Respectfully submitted,

Orest Blaschuk et al.

SEED Intellectual Property Law Group PLLC



Qing Lin, Ph.D.
(See Limited Recognition)

QXL:jab

Enclosures:

Supplemental Information Disclosure Statement
PTO-1449, Cited References (3)
Copy of Limited Recognition Under 37 CFR § 10.9(b).

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

D:\NrPortbl\Manage\JUDIB\310169_1.DOC

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 2-4 have been amended.

2. (Five Times Amended) A cell adhesion modulating agent that:

(a) comprises at least five consecutive amino acid residues of a claudin CAR sequence, said claudin CAR sequence being present in a naturally occurring claudin and having the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate amino acid residues ~~that are present in a naturally occurring claudin~~; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine; and

(b) contains no more than 50 consecutive amino acid residues ~~present within~~ the claudin.

3. (Five Times Amended) A cell adhesion modulating agent that:

(a) comprises at least seven consecutive amino acid residues of a claudin CAR sequence, said claudin CAR sequence being present in a naturally occurring claudin and having the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate amino acid residues ~~that are present in a naturally occurring claudin~~; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine; and

(b) contains no more than 50 consecutive amino acid residues ~~present within~~ the claudin.

4. (Three Times Amended) A cell adhesion modulating agent that:

(a) comprises at least eight consecutive amino acid residues of a claudin CAR sequence, said claudin CAR sequence being present in a naturally occurring claudin and having the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate amino acid residues ~~that are present in a naturally occurring claudin~~; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine; and

(b) contains no more than 50 consecutive amino acid residues ~~present within the claudin~~.